Available online at www.scholarsresearchlibrary.com

Scholars Research Library

***J. Comput. Method. Mol. Design*, 2011, 1 (3): 69-82**
(http://scholarsresearchlibrary.com/archive.html)

ISSN : 2231- 3176
CODEN (USA): JCMMDA

2D QSAR studies of some novel quinazolinone derivatives as antitubercular agents

Rajasekaran Subramaniam*[1], Gopalkrishna Rao[1] and Sanjay Pai.P.N[2]

[1]*Department of Pharmaceutical Chemistry, Al-Ameen College of Pharmacy, Hosur Road, Bangalore*
[2]*Department of Quality Assurance, Al-Ameen College of Pharmacy, Hosur Road, Bangalore*

ABSTRACT

In the present study, quantitative structure activity relationship study was performed on a series of novel quinazolinone derivatives as antitubercular agents using Chem Office ultra 7.0. Multiple linear regression analysis was performed to derive quantitative structure activity relationship models which were further evaluated internally as well as externally for the prediction of activity. The quantitative structure activity relationship evaluation involved a study on thirty four different models; few of them have shown considerable F value. This study indicates that descriptors (logP, ovality, radius and diameter) play an important role for the activity. The data obtained from this present quantitative structure activity relationship study may be useful in the design of more potent substituted quinazolinone derivatives.

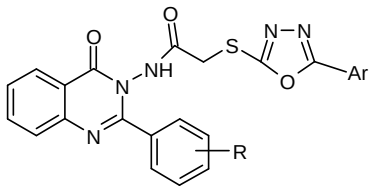
Key words: 2D-QSAR, quinazolinone, antitubercular activity.

INTRODUCTION

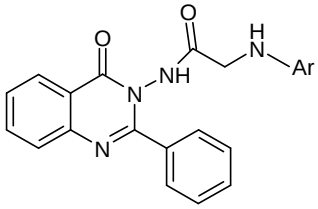
Data from the World Organization of Health show a significant rise in drug-resistant tuberculosis [1–3]. Tuberculosis (TB) is one of the leading causes of death and suffering worldwide among the infectious diseases. The ever-increasing drug resistance, toxicity and side effects of currently used anti-tuberculosis drugs and the absence of their bactericidal activity highlight the need for new, safer and more effective anti-tuberculosis drugs [4–8]. The computer-aided prediction of biological activity in relation to the chemical structure of a compound is now a commonly used technique in drug discovery [9–14]. Modern drug discovery also relies on the interface of chemical and biological diversity through high throughput screening [15].

Quinazolinone ring system has been consistently rewarded as a promising molecule because of its broad spectrum pharmacological activities like antitubercular, antibacterial, antifungal, anticancer, anti-HIV, anti-inflammatory and antihypertensive activities. The quinazolinone moiety is a building block for approximately 150 naturally occurring alkaloids and drugs.

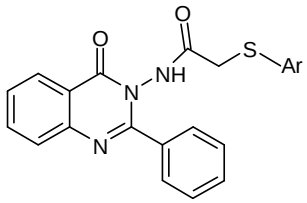
QSAR studies have been widely used to understand the relationship between the structure and biological activity of the molecule. We have reported the synthesis and antitubercular activity of these target compounds [16, 17]. In the present study, QSAR analysis of these substituted quinazolinone derivatives were performed by using multiple linear regression analysis. QSAR studies of these molecules have not been reported earlier. Hence, it was interesting to perform QSAR analysis using Chem Office 7.0 and correlate various physiochemical parameters to the activity for the design of some quinazolinone derivatives [Fig 1].



QO01-QO12



QP01-QP05



QT01-QT02

MATERIALS AND METHODS

Experiments:

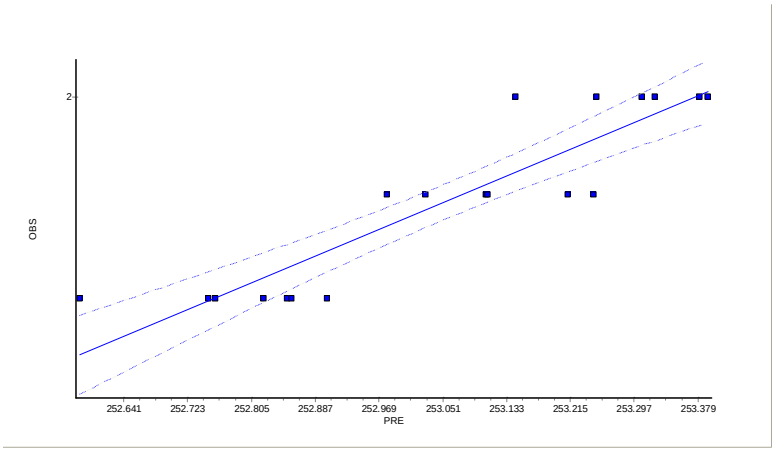
A data set of 19 compounds has been taken from published article. Various descriptors studied are shown in **Table 1**. The values of logMIC have been considered for computational work. All structure of these quinazolinone derivatives were constructed using ChemDraw and transferred to Chem 3D to convert them in to 3D structures. The energy minimization of the molecules was done using MM2 force field followed by semi empirical AMI (Austin model) Hamiltonian method available in MOPAC module by fixing root mean square gradient as 0.1 and 0.0001 kcal/mol. Most stable structure for all the compounds was generated and used for calculating various thermodynamic, steric and electronic descriptors. Values of descriptors with their equation are shown and the values of observed and predicted activity are shown in **Table II**. All the calculated descriptor values were considered as independent variable and biological activity as dependent variable. INSTAT software was used to generate QSAR models by multiple linear regression analysis. Cross validation was performed using leave-one method. Statistical measures used were: n-number of moles in regression, r^2–correlation-coefficient, F-test (Fischer's value) for statistical significance, S-standard deviation.

Table 1: Descriptors considered for the QSAR study:

S.No	Descriptor	Type
1	Heat of formation (HF)	Thermodynamic
2	Boiling Point (BP)	Thermodynamic
3	Critical Pressure (CP)	Thermodynamic
4	Critical Temperature (CT)	Thermodynamic
5	Critical Volume (CV)	Thermodynamic
6	Henry's Law constant (H)	Thermodynamic

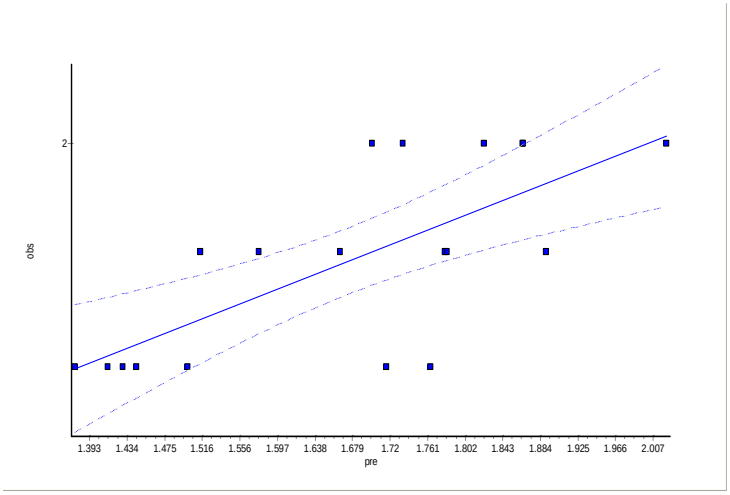
7	Ideal Gas Thermal Capacity (IGTC)	Thermodynamic
8	LogP	Thermodynamic
9	Melting Point (MP)	Thermodynamic
10	Molar Refractivity (MR)	Thermodynamic
11	Standard Gibbs Free Energy (SGFE)	Thermodynamic
12	Connolly Accessible Area (SAS)	Steric
13	Connolly Molecular Area (CMA)	Steric
14	Connolly Solvent-Excluded Volume (SEV)	Steric
15	Ovality (OVA)	Steric
16	Principal Moment of Inertia – X (PMI-X)	Steric
17	Principal Moment of Inertia – Y (PMI-Y)	Steric
18	Principal Moment of Inertia – Z(PMI-Z)	Steric
19	Dipole Moment (D)	Electronic
20	Dipole Moment – X Axis (DX)	Electronic
21	Dipole Moment – Y Axis (DY)	Electronic
22	Dipole Moment – Z Axis (DZ)	Electronic
23	Electronic Energy (EE)	Electronic
24	HOMO Energy (HOMO)	Electronic
25	LUMO Energy (LUMO)	Electronic
26	Repulsion Energy (RE)	Electronic
27	Bend Energy (E_b)	Thermodynamic
28	Charge - Charge Energy (CCE)	Thermodynamic
29	Charge - Dipole Energy (CDE)	Thermodynamic
30	Dipole - Dipole Energy (DDE)	Thermodynamic
31	Non-1,4 VDW Energy (E_v)	Thermodynamic
32	Stretch Energy (SE)	Thermodynamic
33	Stretch-Bend Energy (SEE)	Thermodynamic
34	Torsion Energy (E_t)	Thermodynamic
35	Total Energy (E)	Thermodynamic
36	Van der Waals 1,4 Energy (VDWE)	Thermodynamic

Model 1:



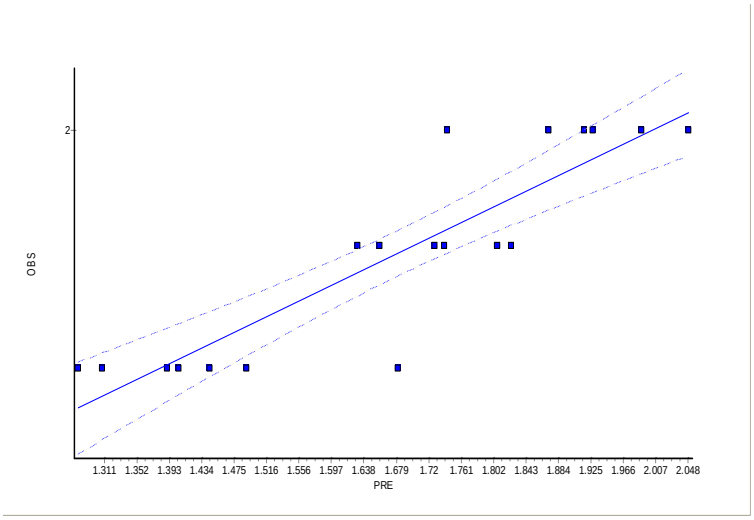
[A:mic] = 125.69 - 0.3433*[B:bend] + 56.244*[C:clsc]+ 0.02870*[D:diam] - 0.9561*[E:log p] + 2.756*[F:MR log]+ 12.809*[G:ovality] - 0.7887*[H:radius] - 56.934*[I:shpA]+ 0.03576*[J:tot energy] + 0.5317*[K:t con] - 0.8917*[L:vdw]
Correlation coefficient (r) = 0.9106, r squared = 0.8293, F = 82.579.
The P value is < 0.0001, considered extremely significant.

Model 3:



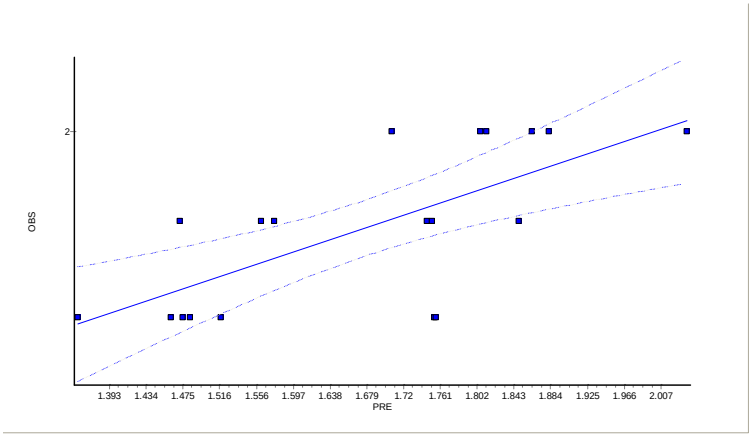
[A:mic] = 2.722 + 0.01179*[B:bend] + 0.02446*[C:clsc]- 0.06882*[D:diam] - 0.2138*[E:logp]
Correlation coefficient (r) = 0.7138, r squared = 0.5096, F = 17.663
The P value is 0.0006, considered extremely significant.

Model 4:



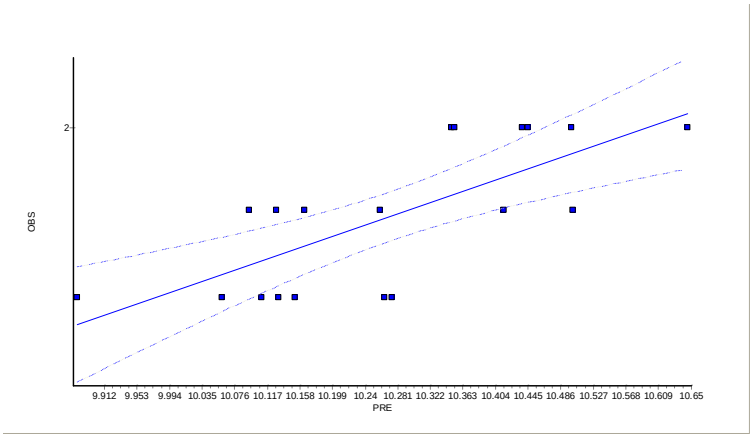
[A:MIC] = 8.526 - 0.1379*[B:log p] + 0.3053*[C:mrlog]- 0.2910*[D:ovality] - 0.1553*[E:parco] - 0.5775*[F:radius]- 3.530*[G:shpc] - 0.1500*[H:es] + 0.007799*[I:tor]+ 0.3172*[J:tcon] + 0.02457*[K:tvcon] - 0.2460*[L:vdw]
Correlation coefficient (r) = 0.8912, r squared = 0.7942, F = 65.600.
The P value is < 0.0001, considered extremely significant.

Model 5:



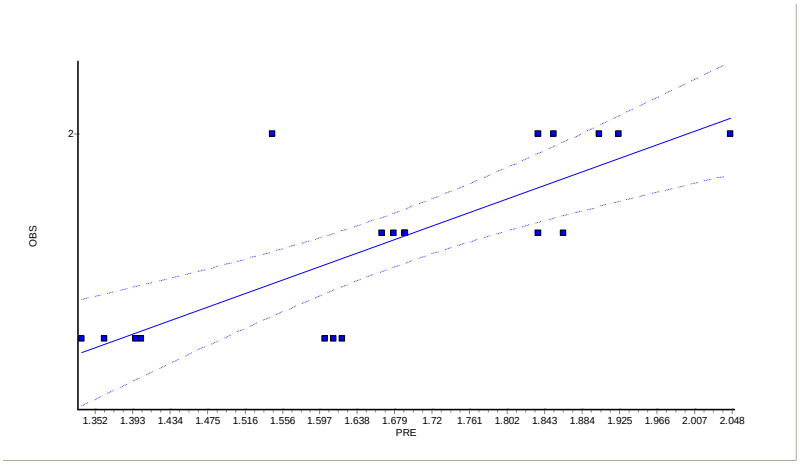
[A:mic] = 1.500 - 0.01651*[B:be] + 0.03426*[C:dpll]- 0.1905*[D:logp] + 0.07903*[E:mr log]
Correlation coefficient (r) = 0.7016, r squared = 0.4923, F = 16.484
The P value is 0.0008, considered extremely significant.

Model 8:



[A:MIC] = 4.323 - 0.8483*[B:homo] + 0.3772*[C:lumo] - 0.1588*[D:log p] + 0.01602*[E:non vdw]
Correlation coefficient (r) = 0.7282, r squared = 0.5303, F = 19.190
The P value is 0.0004, considered extremely significant.

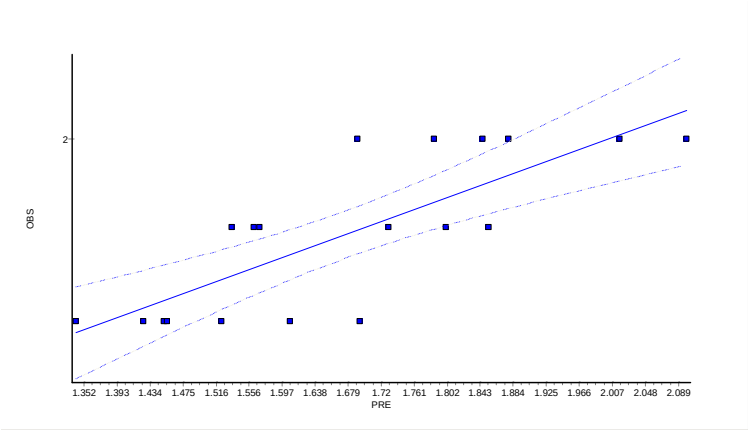
Model 9:



[A:mic] = 0.4442 - 0.05454*[B:diam] + 2.452*[C:ovality] - 0.1812*[D:parco] - 0.2159*[E:radius]
Correlation coefficient (r) = 0.7823, r squared = 0.6120, F = 26.814
The P value is < 0.0001, considered extremely significant.

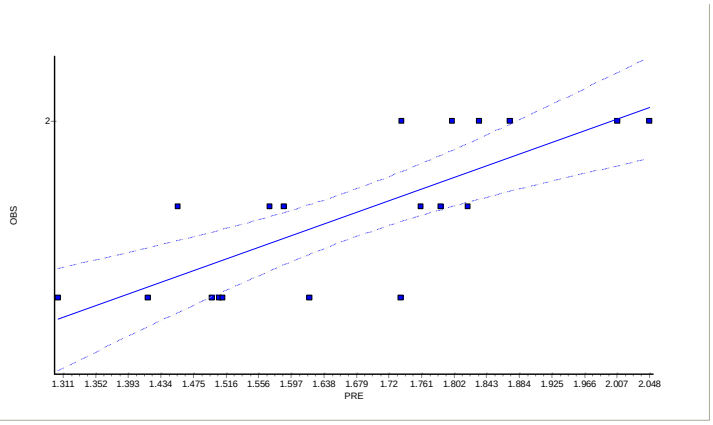
	B:	C:	D:	E:
B:diam	1.0000			
C:ovality	0.9086	1.0000		
D:parco	-0.3421	-0.1912	1.0000	
E:radius	0.9222	0.7941	-0.4529	1.0000

Model 11:



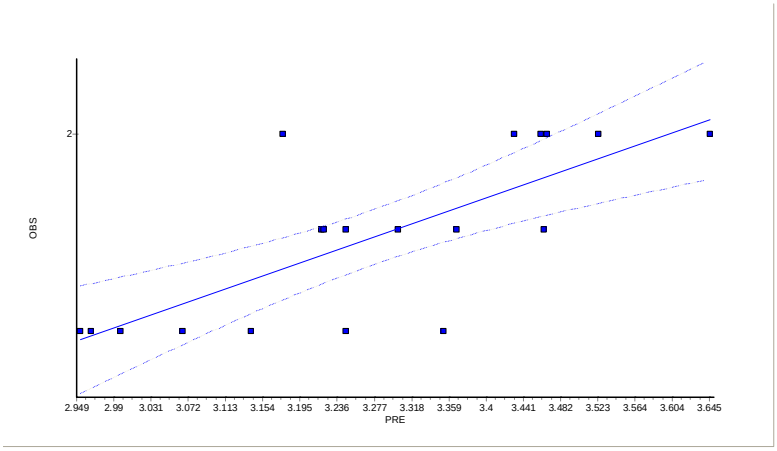
[A:MIC] = 4.281 - 0.09114*[B:log P] - 1.782*[C:ovality]- 0.08130*[D:parco] + 1.731*[E:shpC] - 0.3317*[F:es]- 0.06154*[G:tor] - 0.1468*[H:tcon]
Correlation coefficient (r) = 0.7883, r squared = 0.6214, F = 27.907
The P value is < 0.0001, considered extremely significant.

Model 12:



[A:MIC] = 6.884 - 3.273*[B:ovality] - 0.1598*[C:parco]+ 1.119*[D:shpC] - 0.3779*[E:es] - 0.06445*[F:tor]
Correlation coefficient (r) = 0.7691, r squared = 0.5914, F = 24.610
The P value is 0.0001, considered extremely significant.

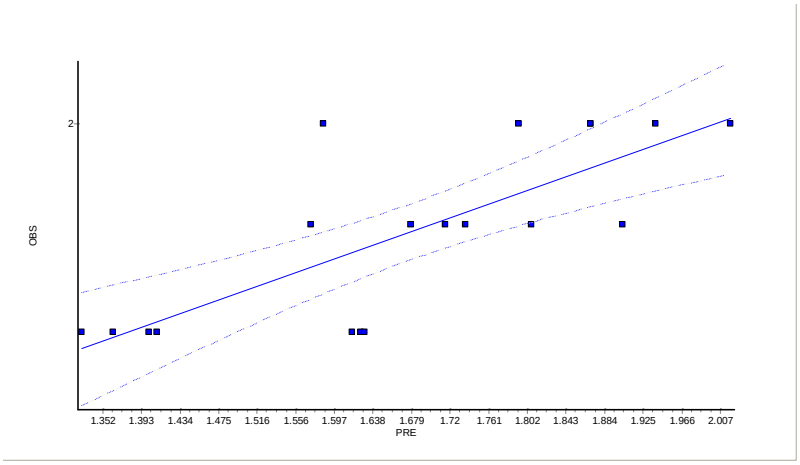
Model 23:



[A:MIC] = 0.7996 - 0.1674*[B:diam] + 3.165*[C:ovality]- 0.1635*[D:parco]
Correlation coefficient (r) = 0.7504, r squared = 0.5631, F = 21.912
The P value is 0.0002, considered extremely significant.

	B:	C:	D:
B:diam	1.0000		
C:ovality	0.9086	1.0000	
D:parco	-0.3421	-0.1912	1.0000

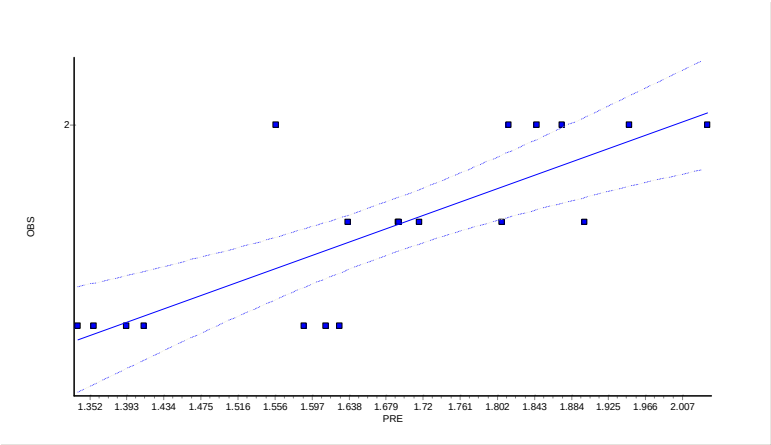
Model 25:



[A:MIC] = 3.744 + 0.01335*[B:diam] - 0.1736*[C:parco] - 0.2389*[D:rad]
Correlation coefficient (r) = 0.7707, r squared = 0.5940, F = 24.875
The P value is 0.0001, considered extremely significant.

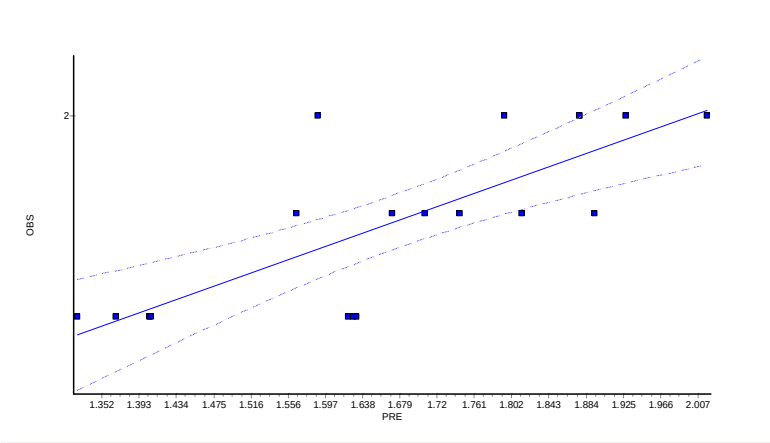
	B:	C:	D:
B:diam	1.0000		
C:parco	-0.3421	1.0000	
D:rad	0.9222	-0.4529	1.0000

Model 26:



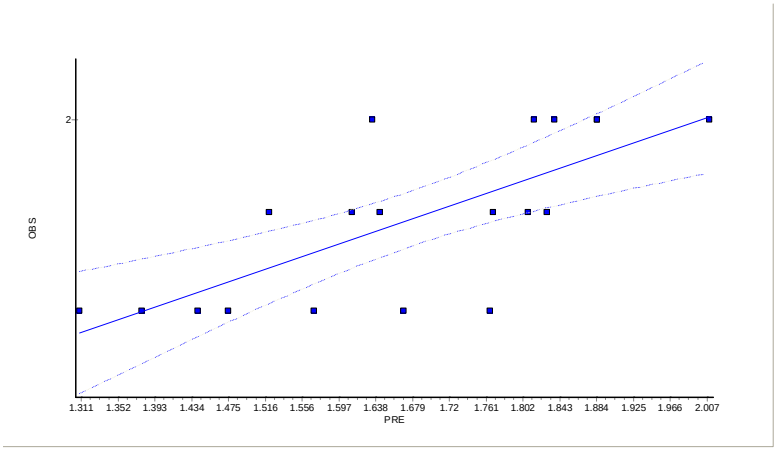
[A:MIC] = 1.874 + 1.387*[B:ovality] - 0.1807*[C:parco] - 0.2731*[D:rad]
Correlation coefficient (r) = 0.7783, r squared = 0.6057, F = 26.118
The P value is < 0.0001, considered extremely significant.

Model 28:



[A:MIC] = 3.746 - 0.1721*[B:parco] - 0.2138*[C:rad]
Correlation coefficient (r) = 0.7702, r squared = 0.5932, F = 24.791
The P value is 0.0001, considered extremely significant.

Model 31:



[A:MIC] = 3.420 - 0.09302*[B:diam] - 0.1508*[C:parco]
Correlation coefficient (r) = 0.7295, r squared = 0.5322, F = 19.342
The P value is 0.0004, considered extremely significant.

Table II: Comparison of observed activity with predicted activity

	OBSERVED ACTIVITY	PREDICTED ACTIVITY									
Compd		MODEL 1	MODEL 2	MODEL 3	MODEL 4	MODEL 5	MODEL 6	MODEL 7	MODEL 8	MODEL 9	MODEL 10
QO01	2.00	253.24	1.73	1.86	1.98	1.80	1.83	88798.20	10.35	1.92	1.93
QO02	1.38	252.75	1.61	1.76	1.27	1.75	1.75	94886.78	10.26	1.62	1.62
QO03	2.00	253.14	1.67	1.70	1.74	1.70	1.70	94436.82	10.34	1.54	1.66
QO04	1.70	253.10	1.60	1.78	1.80	1.74	1.75	95172.23	10.25	1.86	1.78
QO05	1.38	252.90	1.69	1.71	1.68	1.75	1.76	94744.68	10.27	1.61	1.59
QO06	2.00	253.38	1.69	2.02	2.04	2.03	2.01	105164.6	10.64	2.04	1.59
QO07	1.70	253.10	1.71	1.57	1.72	1.56	1.60	88814.93	10.16	1.69	1.71
QO08	1.38	252.85	1.64	1.49	1.44	1.48	1.52	94731.79	10.11	1.60	1.48
QO09	1.38	252.82	1.67	1.41	1.30	1.46	1.47	94341.79	10.15	1.33	1.42
QO10	1.70	252.97	1.64	1.51	1.65	1.47	1.52	94847.49	10.12	1.67	1.73
QO11	1.38	252.74	1.69	1.42	1.49	1.51	1.53	94567.49	10.06	1.40	1.71
QO12	2.00	253.39	1.67	1.73	1.92	1.86	1.85	105038.1	10.49	1.83	1.80
QP 01	2.00	253.30	1.81	1.82	1.87	1.81	1.81	72138.63	10.43	1.90	1.79
QP 02	2.00	253.32	1.83	1.86	1.91	1.88	1.87	72975.40	10.44	1.85	1.83
QP 03	1.70	253.24	1.78	1.89	1.82	1.84	1.80	78218.85	10.50	1.68	1.86
QP 04	1.70	253.02	1.76	1.78	1.74	1.75	1.73	77060.68	10.41	1.83	1.81
QP 05	1.38	252.85	1.71	1.44	1.38	1.47	1.51	89944.75	10.13	1.39	1.57
QT 01	1.70	253.21	1.43	1.66	1.63	1.57	1.48	121092.4	10.09	1.66	1.38
QT 02	1.38	252.58	1.43	1.37	1.40	1.35	1.28	120995.0	9.877	1.36	1.49

Table II: Comparison of observed activity with predicted activity

	OBSERVED ACTIVITY	PREDICTED ACTIVITY									
Compd		MODEL 11	MODEL 12	MODEL 13	MODEL 14	MODEL 15	MODEL 16	MODEL 17	MODEL 18	MODEL 19	MODEL 20
QO01	2.00	2.01	2.00	1.60	1.80	1.73	1.69	1.67	1.79	1.69	1.80
QO02	1.38	1.52	1.51	1.60	1.74	1.68	1.50	1.70	1.70	1.52	1.79
QO03	2.00	1.69	1.73	1.72	1.74	1.78	1.67	1.66	1.74	1.69	1.74
QO04	1.70	1.56	1.58	1.61	1.80	1.71	1.53	1.71	1.77	1.53	1.81
QO05	1.38	1.69	1.73	1.70	1.74	1.80	1.65	1.65	1.74	1.68	1.76
QO06	2.00	2.09	2.04	1.69	1.99	2.04	1.63	1.62	2.01	1.65	1.99
QO07	1.70	1.72	1.81	1.60	1.64	1.60	1.69	1.68	1.61	1.72	1.68
QO08	1.38	1.60	1.62	1.60	1.58	1.55	1.69	1.61	1.62	1.59	1.54
QO09	1.38	1.45	1.50	1.70	1.55	1.65	1.65	1.65	1.54	1.69	1.60
QO10	1.70	1.56	1.57	1.59	1.59	1.58	1.66	1.57	1.65	1.53	1.54
QO11	1.38	1.45	1.49	1.69	1.56	1.67	1.63	1.63	1.55	1.66	1.62
QO12	2.00	1.87	1.83	1.68	1.81	1.90	1.61	1.62	1.80	1.66	1.87
QP 01	2.00	1.78	1.80	1.81	1.79	1.72	1.79	1.77	1.80	1.80	1.67
QP 02	2.00	1.84	1.87	1.83	1.84	1.72	1.83	1.81	1.84	1.84	1.69
QP 03	1.70	1.85	1.78	1.85	1.77	1.65	1.85	1.84	1.77	1.87	1.61
QP 04	1.70	1.80	1.76	1.81	1.75	1.68	1.79	1.78	1.74	1.82	1.64
QP 05	1.38	1.42	1.41	1.59	1.40	1.42	1.67	1.61	1.41	1.62	1.43
QT 01	1.70	1.53	1.45	1.54	1.42	1.51	1.58	1.58	1.40	1.59	1.56
QT 02	1.38	1.34	1.30	1.56	1.29	1.37	1.62	1.62	1.27	1.63	1.42

Table II: Comparison of observed activity with predicted activity

	OBSERVED ACTIVITY	PREDICTED ACTIVITY									
Compd		MODEL 21	MODEL 22	MODEL 23	MODEL 24	MODEL 25	MODEL 26	MODEL 27	MODEL 28	MODEL 29	MODEL 30
QO01	2.00	1.60	1.59	3.43	1.66	1.93	1.94	1.65	1.92	1.68	1.81
QO02	1.38	1.52	1.60	3.35	1.67	1.61	1.58	1.67	1.63	1.64	1.76
QO03	2.00	1.74	1.74	3.17	1.62	1.58	1.55	1.61	1.58	1.63	1.73
QO04	1.70	1.53	1.60	3.36	1.66	1.90	1.89	1.65	1.89	1.69	1.79
QO05	1.38	1.74	1.74	3.24	1.61	1.62	1.61	1.61	1.62	1.61	1.76
QO06	2.00	1.74	1.73	3.64	1.61	2.01	2.03	1.61	2.01	1.60	2.01
QO07	1.70	1.60	1.59	3.22	1.66	1.71	1.71	1.65	1.70	1.68	1.67
QO08	1.38	1.60	1.56	3.14	1.66	1.63	1.62	1.65	1.62	1.68	1.61
QO09	1.38	1.74	1.74	2.99	1.61	1.36	1.33	1.61	1.36	1.61	1.59
QO10	1.70	1.59	1.55	3.21	1.65	1.67	1.69	1.65	1.67	1.66	1.65
QO11	1.38	1.74	1.74	3.06	1.61	1.40	1.39	1.61	1.40	1.60	1.61
QO12	2.00	1.74	1.74	3.46	1.60	1.79	1.81	1.61	1.79	1.59	1.87
QP 01	2.00	1.77	1.77	3.52	1.80	1.86	1.87	1.81	1.87	1.78	1.64
QP 02	2.00	1.77	1.78	3.46	1.81	1.86	1.84	1.81	1.87	1.81	1.64
QP 03	1.70	1.78	1.79	3.30	1.82	1.73	1.69	1.81	1.74	1.82	1.55
QP 04	1.70	1.77	1.78	3.46	1.80	1.80	1.80	1.81	1.81	1.78	1.60
QP 05	1.38	1.60	1.57	2.96	1.65	1.40	1.41	1.65	1.40	1.66	1.47
QT 01	1.70	1.59	1.58	3.24	1.63	1.57	1.63	1.65	1.56	1.60	1.58
QT 02	1.38	1.59	1.59	2.95	1.64	1.32	1.35	1.65	1.32	1.63	1.42

Table II: Comparison of observed activity with predicted activity

	OBSERVED ACTIVITY	PREDICTED ACTIVITY			
Compd		MODEL 31	MODEL 32	MODEL 33	MODEL 34
QO01	2.00	1.83	1.83	1.67	1.66
QO02	1.38	1.76	1.77	1.67	1.66
QO03	2.00	1.63	1.71	1.65	1.61
QO04	1.70	1.80	1.84	1.69	1.66
QO05	1.38	1.66	1.71	1.63	1.61
QO06	2.00	2.00	1.98	1.61	1.61
QO07	1.70	1.64	1.67	1.67	1.66
QO08	1.38	1.57	1.61	1.67	1.66
QO09	1.38	1.44	1.52	1.63	1.61
QO10	1.70	1.61	1.61	1.65	1.66
QO11	1.38	1.47	1.52	1.61	1.61
QO12	2.00	1.81	1.78	1.59	1.61
QP 01	2.00	1.88	1.77	1.77	1.81
QP 02	2.00	1.88	1.83	1.81	1.81
QP 03	1.70	1.76	1.76	1.83	1.81
QP 04	1.70	1.82	1.73	1.77	1.81
QP 05	1.38	1.37	1.41	1.65	1.66
QT 01	1.70	1.51	1.42	1.57	1.66
QT 02	1.38	1.30	1.30	1.61	1.66

RESULTS AND DISCUSSION

The QSAR model was performed on thirty four different models and the results have been verified. Of all the models studied, models 1,3,4,8,9,11,12,23,26,28 and 31 comprising of bend energy, cluster count, diameter, log P, molar refractivity, ovality, radius, shape attribute, total energy, total connectivity and Vanderwaal's energy have been found to be extremely significant showing the importance of these descriptors in the designing of novel quinazolinone analogs for antitubercular activity, the models 6,10,14,15,18,20,30, and 32 were found to be significant while the models 2,7,13,17,19,21,22,24,27,29,33 and 34 were not significant for the biological activity. Hence the physicochemical parameters highlighted in the models 1, 4,9,11 and 26 can be considered while designing novel quinazolinone derivatives for antitubercular activity. Since the compounds QO02, QO05, QO08, QO09, QO11, QP05 and QT02 showed good antitubercular activity these compounds were subjected to drug likeness and drug score evaluation. It was interesting to find that the compounds QO02 and QO05 had a drug score similar to Sparfloxacin and Ciprofloxacin.

CONCLUSION

Out of 34 computational models studied, 9 of them were found to be extremely significant. The model 9 with descriptors involving diameter, ovality, partition coefficient and radius was found to be extremely significant. Also the model 26 with ovality, partition coefficient and radius was found to be extremely significant implying the importance of these parameters for the design of new pharmacophores containing quinazolinone moiety for antitubercular activity.

Acknowledgements
The authors are thankful to Prof. B.G.Shivananda, Principal, Al-Ameen College of Pharmacy, Bangalore for providing the facilities to carry out this research work.

REFERENCE

[1] World Health Organization. In Anti-tuberculosis Drug Resistance in the World; The WHO/IUATLD global project on anti-tuberculosis drug resistance surveillance, **1997**.
[2] I Bastian; R Colebunders. *Drugs*, **1999**, 58, 633.
[3] D Butler. *Nature*, **2000**, 406, 670.
[4] C K Bodiang. *Scott. Med. J*, **2000**, 45, 25.
[5] R E Van Scoy; C J Wilkowske; *Mayo Clin. Proc*. **1999**, 74, 1038.
[6] R Long. *Can. Med. Assoc. J*. **2000**, 63, 425.
[7] A Gazdic. *Med. Arch*. **1998**, 52, 207.
[8] A Pozniak. *Int. J. Tuberc. Lung Dis*, **2000**, 4, 993.
[9] V V Poroikov; D A Filimonov; Y V Borodina. *J. Chem. Inf. Comput. Sci*, **2000**, 40, 1349.
[10] A V Stepanchikova; A A Lagunin; D A Filimonov, V V Poroikov, *Curr. Med. Chem*, **2003**, 10, 225.
[11] V V Poroikov; D A Filimonov; *J. Comput. Aided Mol.Des*. **2003**, 16, 819.
[12] A A Geronikaki; J C Dearden; D Filimonov; I Galaeva; T L Garibova; T Gloriozova; V Krajneva; A Lagunin; F Z Macaev; G Molodavkin; V V Poroikov; S I Pogrebnoi; F Shepeli; T A Voronina; M Tsitlakidou; L Vlad. *J. Med. Chem*, **2004**, 47, 2870.
[13] A Geronikaki; E Babaev; J Dearden; W Dehaen; D Filimonov; I Galaeva; V Krajneva; A Lagunin; F Macaev; G Molodavkin; V Poroikov; S Pogrebnoi; V Saloutin; A Stepanchikova; E Stingaci; N Tkach; L Vlad; T Voronina. *Bioorg. Med. Chem*, **2004**, 12, 6559.
[14] E E Oruc; S Rollas; F Kandemirli; N Shvets; A S Dimoglo. *J. Med. Chem*, **2004**, 47, 6760.
[15] L Collins; S G Franzblau; *Antimicrob. Agents Chemother*, **1997**, 41, 1004.
[16] GopalKrishna Rao; S Rajasekaran; P N Sanjay Pai. *Indian J Hetero Chem.*, **2010**, 19, 293.
[17] S Rajasekaran; GopalKrishna Rao; P N Sanjay Pai. *Der Pharma Chemica*, **2010**, 2(5), 153.